ASTRA®
Astra Pharmaceuticals

April 15, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fisher's Lane
Room 1061
Rockville, MD 20852

9011 '99 APR 20 P2:18

Re: "Bioanalytical Methods Validation for Human Studies"

Dear Sir or Madam:

Reference is made to the January 5, 1999 Federal Register notice announcing the availability of a Draft Guidance for Industry entitled "Bioanalytical Methods Validation for Human Studies".

We have carefully reviewed this draft guidance and have some comments and suggestions with regard to the guidance. Attached is a list of our comments.

Thank you for your consideration.

Sincerely,

Elizabeth Fenna
Regulatory Intelligence Partner
Regulatory Affairs

C35

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"Guidance for Industry: Bioanalytical Methods Validation for Human Studies"

Comments submitted by Astra Pharmaceuticals, LP, 725 Chesterbrook Blvd., Wayne, PA 19087

Page/line number	Comments
Page i, line 6, page 2, line 4, page 3, line 27and 30 and page 9, line 14	We suggest that the word "specificity" be changed to "selectivity" throughout the entire document to more accurately reflect current terminology. See reference J. Vessman, J. Pharm. Biomed. Anal. 14 (1996) 867-869.
Page 3, line 30.	We suggest that the underlined section below be excluded....."For selectivity ~~specificity~~ , analyses of blank samples of the appropriate biological matrix (plasma, urine, or other matrix) should be obtained from six individuals under controlled conditions, with reference to time of day, food ingestion, and other factors considered important in the intended study". Using today's tandem mass spectrometry as a selective detector, there is no need to analyze blank plasma from the intended study in advance. In addition, it is most often not possible to obtain blank plasma from the intended study in advance for methods validation.
Page 4, line 11	We suggest that the following change be made: "Potential interference from nicotine and common OTC drugs and metabolites, such as caffeine, aspirin, acetaminophen, and ibuprofen should be routinely tested." to "Potential interference from nicotine and common OTC drugs and metabolites such as caffeine, aspirin, acetaminophen, and ibuprofen should be **considered**." Today more and more bioanalysis is performed using selective tandem mass spectrometry for detection. With such a selective detector, the tedious work to routinely test interference from all the metabolites of for example, acetaminophen, is not always required or appropriate.

Page 4, line 18-19	We suggest that the following change be made: "A calibration curve should be prepared in the same biological matrix as the samples..." to "A calibration curve should be prepared in the same biological matrix, **if possible**, as the samples" It can sometimes be very difficult to find blank matrix of, for example, cerebrospinal fluid and some types of tissues.
Page 4, line 27	We suggest that the following change be made: "....processed with internal standard) and five <u>to eight</u> non-zero samples" to "...processed with internal standard) and at least five non-zero samples" This also applies to page 6 line 18. More than eight non-zero standard samples can be necessary when the range is wide and the regression equation is more complex.
Page 5, line 7-8	We suggest that the following change be made: "The simplest workable regression equation <u>should be used with minimal or no weighting. Selection of weighting and use of a complex regression equation</u> should be justified" to "Selection of a workable regression equation and weighting should be justified." A more complex regression equation can often produce much better accuracy data and should therefore be considered.
Page 6, line 10.	We suggest that the following change be made: "...the extent of recovery of an analyte and/or the internal standard may be <u>as</u> low <u>as 50 to 60 %</u>...." to" .....the extent of recovery of an analyte and/or the internal standard may be **low**.....". Adequate reproducibility data can be obtained even with a recovery lower than 50% if an optimal, e.g. deuterium-labeled, internal standard is used.
Page 6, line 16	We suggest that the following change be made: "Pre-study validation of an analytical method should be carried out using at least three batches of biological matrix, where each batch is collected from a different source. Each batch should contain....." to..... "Pre-study validation of an analytical method should be carried out using at least three batches of biological matrix, where each batch is collected from a different source. One batch of plasma should be used for quality control samples and the other two batches of plasma should be used for calibration curves. Each validation batch should contain....." This validation design will better reveal possible differences between the plasma batches.

Page 7, line 13	We suggest that the following change be made: "....and short-term (bench top, room temperature and conditions) storage..." to "...and short-term (intended bench top conditions) storage..."
Page 8, line 13	We suggest that the following change be made: "The volume of samples...." to "The **number** of samples...." Each sample should only be analyzed once.
Page 10, line 11	We suggest that the following change be made: "All study samples from a subject should be analyzed in a single run, **if possible."** In steady-state studies, the first samples may have to be analyzed before the last samples have been taken from the patient.
Page 10, line 30	We suggest that the following sentence be excluded....."Reassays should be done in triplicate....." The volume of plasma or biological matrix will seldom be enough to reassay in triplicate.
Page 11-12	We question the following: "Documentation for submission to the Agency should include: Complete serial chromatograms of 20% of subjects, with standards and QC samples." Does this mean that these chromatograms should be submitted to FDA without a formal request from the Agency? This documentation can be voluminous.

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